--26. (new) The dendritic cell preparation according to claim 18 containing CD-40 ligand.--

--27. (new) The dendritic cell preparation according to claim 20 wherein the compound is CD-40 ligand.--

--28. (new) The dendritic cell preparation according to claim 22 wherein the compound is CD-40 ligand.--

REMARKS

The specification has been amended to revise the title, update related application data and correct errors and omissions as requested by the Examiner.

Status of the Claims

Applicants have amended claims 9, 10 and 11, and added new claims 15-28. Claims 8-11 and 15-28 are pending. For the convenience of the Examiner, a copy of the pending claims is presented as an appendix. No new matter is presented by these amendments. New claims 15 and 16 are based on, *inter alia*, claims 10 and 11, as filed. New claims 17-25 find support in the specification as filed at, for example, page 13, line 26.

Claims 8-11 are rejected under 35 U.S.C. §112, first paragraph, and §§ 102(e) and 103(a). Claims 12-13 have been withdrawn from consideration by the Examiner. Applicants reserve the right to pursue all avenues of appeal, including petition, regarding the finality of the restriction requirement excluding the subject matter of claims 12-13 from examination in the instant application.

Information Disclosure Statement

Pursuant to the Examiner's request, copies of the references cited on the Information Disclosure Statement that were misplaced by the Office and unavailable to the Examiner are enclosed herewith.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 9 and 11 are rejected under 35 U.S.C. § 112, first paragraph, as the Examiner asserts that CD40 binding proteins other than CD40 ligand and CD40 antibodies are not

enabled by the specification. Claims 9 and 11 have been amended to recite "CD40 antibody and CD40 ligand". Accordingly, Applicants submit that the rejection has been obviated.

Steinman Does Not Anticipate or Render Obvious The Claims

Claims 8-11 are rejected under 35 U.S.C. § 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a) as obvious over Steinman et al. (U.S. Patent No. 5,851,756). The Examiner notes that although Steinman does not disclose flt3-ligand and CD40 binding proteins, Steinman does teach dendritic cell populations including antigen pulsed and transfected cell populations. The Examiner states that the patentability of a product does not depend on its method of production, and asserts that the claimed functional limitations would be inherent properties of the referenced dendritic cell populations. Applicants respectfully traverse this rejection.

Steinman discloses that GM-CSF is a factor which modulates the maturation and function of dendritic cells (col. 2, lines 42-44). Steinman teaches culturing cells in the presence of GM-CSF at a concentration sufficient to promote the survial and proliferation of dendritic cell precursors (col. 13, line 67 to col. 14, line 3). Steinman states that it "may be desirable to include additional cytokines in the culture medium in addition to GM-CSF." The cytokines enumerated by Steinman are G-CSF, M-CSF, IL-1α, IL-1β, IL-3, IL-6, TNFα and SCF. None of these cytokines is flt3-ligand. Further, the use of GM-CSF to culture dendritic cells is taught as a crucial aspect by Steinman (col. 28, lines 61-64).

In fact, the claimed dendritic cell populations and preparations do indeed appear to be different than the cited dendritic cell populations of Steinman. As evidence that the nature of such dendritic cell populations differ from dendritic cell populations produced by contacting hematopoietic stem or progenitor cells with flt3-ligand, Applicants draw the Examiner's attention to: Exhibit A—a publication by Pulendran *et al.*, 1999, Proc. Natl. Acad. Sci. USA 96:1036-1041, entitled "Distinct dendritic cell subsets differentially regulate the class of immune response *in vivo*"; and Exhibit B—a submitted manuscript by Brasel *et al.* entitled "Generation of murine dendritic cells from flt3-ligand-supplemented bone marrow cultures".

Pulendran *et al.* show that the populations of dendritic cells produced *in vivo* by contact with flt3-ligand differ from those produced *in vivo* by contact with GM-CSF. Figure 1 on page 1037 illustrates phenotypic differences between the two populations of cells. Specifically, in flt3-ligand treated mice, the lymphoid related dendritic cells are more

prevalent than the myeloid related dendritic cells, while in GM-CSF treated mice, the myloid subset of dendritic cells dominate. These data are also discussed in the DISCUSSION section at page 1040, column 1, second full paragraph. A similar trend has also been observed for *in vitro* cultured dendritic cell populations. In the manuscript by Brasel *et al.*, submitted to the journal "Blood", the authors compared dendritic cells using bone marrow cultures supplemented with either flt3-ligand for nine days, or GM-CSF plus IL-4 for seven days (IL-4 is well established as an additive to GM-CSF dendritic cell culture in order to prevent the outgrowth of monocytes to macrophages ; see Sallusto *et al.*, 1994, J. Exp. Med. 179:1109 and Labeur *et al.*, 1999, J. Immun. 162:168). Again, unlike the GM-CSF and IL-4 generated dendritic cells, the flt3-ligand generated dendritic cell populations expressed phenotypes of both lymphoid-type and myeloid-type dendritic cells (see pages 10-11 of the manuscript). The GM-CSF and IL-4 generated dendritic cell populations had a more myeloid-type phenotype (*Id.*).

In other words, the flt3-ligand generated dendritic cell populations had at least two different "flavors" of dendritic cells; both myloid and lymphoid, while IL-4/GM-CSF generated dendritic cell populations have predominately only the myleloid "flavor." As the lymphoid dendritic cells are better at driving TH1 responses, such flt3-ligand generated dendritic cells would be expected to be more useful in immunotherapy applications. Thus, the flt3-ligand generated dendritic cell populations have significant advantages over the GM-CSF/IL-4 generated dendritic cell populations.

In view of the above, Applicants submit that they have demonstrated a patentable distinction between the GM-CSF generated dendritic cells of the cited art, and the claimed invention. Accordingly, Applicants request withdrawal of the rejection based upon Steinman.

The Invention, As Claimed, Is NonObvious Over Steinman In View Of Lyman And Inaba And/Or Further In View Of Gruss And/Or Caux

Claims 8-11 are rejected under 35 U.S.C. § 103(a) as obvious over Steinman in view of Lyman and Inaba and/or further in view of Gruss and/or Caux. Steinman is cited for disclosure of dendritic cell populations, although the Examiner notes that Steinman does not disclose flt3-ligand or CD40 binding proteins in expanding dendritic cell populations. The Examiner cites Lyman for teaching the use of flt3-ligand to stimulate the proliferation of both hematopoietic and non-hematopoietic stem cells. Inaba is cited for the teaching that

granulocytes, macrophages and dendritic cells can arise from a common hematopoietic progenitor. Then, because GM-CSF provides stimulatory activity to stem cells and to dendritic cells, the Examiner asserts that a combination of flt3-ligand and GM-CSF would have been expected to stimulate various hematopoietic cells including dendritic cells. Applicants traverse.

To establish a case of prima facie obviousness under 35 U.S.C. § 103, a combination of references must: (1) suggest to those of ordinary skill in the art that they should make the claimed invention, and (2) reveal to those of ordinary skill in the art that they would have a reasonable expectation of success. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in Applicant's disclosure. *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). Evidence that supports, rather than negates, patentability must also be fairly considered. *Id.* at 1532. In the present case, the combined cited art does not teach or suggest the claimed invention. Moreover, no reasonable expectation of success in achieving the claimed invention is found in the cited art.

The Claimed Invention Is Not Taught Or Suggested By The Cited Art

The claims as pending are directed to preparations of dendritic cells, and dendritic cell populations, produced by contacting hematopoietic cells with flt3-ligand. At the outset, Applicants point out that the Examiner appears to have asserted only that the cited art renders obvious generate dendritic cell populations produced using flt3-ligand **in combination with** GM-CSF (Office Action, page 5, fourth full paragraph); however, this combination is only one aspect of the claimed invention. Moreover, as discussed above, the flt3-ligand generated dendritic cell populations are different in kind from those generated with only GM-CSF, and possess distinct and unexpected advantages over the GM-CSF-generated dendritic cell populations of Steinman. Namely, the flt3-ligand generated dendritic cell populations have significant numbers of **both** myloid-like and lymphoid-like dendritic cells.

As stated in the Steinman patent cited by the Examiner, dendritic cells are a rare cell type, of which very few are normally found in any given organ. For example, only about 0.1% of the white cells in human blood are dendritic cells (col. 1, lines 55-69). None of the cited references disclose that flt3-ligand should be used to generate dendritic cells, as opposed to the wide variety of other, often more common, hematopoietic cells including but not

limited to erythrocytes, platelets, neutrophils, monocytes, macrophages, eosinophils, basophils, mast cells, B cells and T cells.

Inaba does not provide the motivation to make dendritic cells as in Steinman using the flt3-ligand taught by Lyman. Simply because GM-CSF stimulates the growth of certain stem cells and dendritic cells, does not suggest that **all** other hematopoietic growth facts will also stimulate the growth of stem and dendritic cells. The rejection appears to be on the basis that, if one cytokine is shown to stimulate growth of dendritic cells (in this case, GM-CSF), then it would be obvious that ***all cytokines*** would do so. Such a basis for a rejection presents, in essence, an "obvious to experiment" standard for obviousness, which is not the law. *In re Dow Chemical Co.*, 5 USPQ2d at 1532.

Grusse and Caux do not cure the deficiencies of the primary references. In particular, none of these references teach or suggest the missing aspect of the claimed invention that dendritic cell populations can be produced by contacting hematopoietic cells with flt3-ligand.

The Cited Art Provides No Reasonable Expectation Of Success

In fact, the rarity of dendritic cells noted in Steinman implies exactly the opposite conclusion-- that only a unique set of conditions will stimulate growth of progenitor cells into dendritic cells. Thus, for any newly identified hematopoietic cytokine, one of skill in the art would have no reasonable expectation of success in using that cytokine, alone or in combination, to achieve preparations of dendritic cells. Moreover, given that Steinman teaches that the use of GM-CSF is "crucial", the combination of references cited by the Examiner would teach away from using flt3-ligand, alone or in combination with other cytokines that are not GM-CSF.

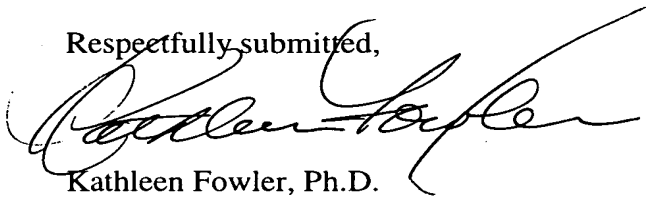
Steinman, Lyman, Inaba, *etc* may, at best, provide an invitation to experiment. But invitations to experiment fall woefully short of a *prima facie* case of obviousness. The combination of Steinman, Lyman, Inaba, Grusse and Caux simply does not rise to the level of a reasonable expectation that flt3-ligand can be used to generate a unique population of dendritic cells. A reasonable expectation of success with respect to the claimed invention arose only in view of Applicants' disclosure.

In view of the above discussion, Applicants respectfully request that the rejection for obviousness be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants submit that the claims of the present application are in condition for allowance and respectively request a notice to that effect. If the Examiner believes that any issues still outstanding could be resolved, or if the prosecution of the application could be expedited, by a telephone conference, Applicants invite the Examiner to telephone the undersigned at (206) 470-4847.

Respectfully submitted,



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